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FIFTEEN SYMPOSIA ON MICRODOSIMETRY: IMPLICATIONS FOR MODERN PARTICLE-BEAM CANCER RADIOTHERAPY

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The objective of microdosimetry was, and still is, to identify physical descriptions of the initial physical processes of ionising radiation interacting with biological matter which correlate with observed radiobiological effects with a view to improve the understanding of radiobiological mechanisms and effects. The introduction of therapy with particles starting with fast neutrons followed by negative pions, protons and light ions necessitated the application of biological weighting factors for absorbed dose in order to account for differences of the relative biological effectiveness (RBE). Dedicated radiobiological experiments in therapy beams with mammalian cells and with laboratory animals provided sets of RBE values which are used to evaluate empirical 'clinical RBE values'. The combination of such experiments with microdosimetric measurements in identical conditions offered the possibility to establish semi-empirical relationships between microdosimetric parameters and results of RBE studies.

INTRODUCTION

Microdosimetry in its original meaning started more than 50 y ago with the development and the use of low-pressure, tissue-equivalent proportional counters by H.H. Rossi ('Rossi Counters') (Figure 1)[(1)]. The European Commission made Microdosimetry a priority in its radiation protection research programme of EURATOM and initiated in 1967 the series of the by now 15 Microdosimetry Symposia.

Experimental microdosimetry with Rossi Counters enables the measurement and quantification of the energy imparted by single primary particles ('single events') in microscopic volumes with dimensions similar to that of biological entities such as cells or cell nuclei. More precisely, the counters simulate biological matter of linear dimensions of the order of micrometre by using tissue-equivalent material for the counter walls and low-pressure tissue-equivalent counting gas. The pulse-height distributions correspond to energy deposition distributions in the simulated microscopic volume. This technique provided a new set of data that could be compared with data obtained in LET computation developed at the same period. More detailed information on the technique and recent developments of it are given by L. Braby (this Symposium).

APPLICATIONS OF MICRODOSIMETRY

The first microdosimetry symposium in 1967 focused on work of Harald Rossi and his team[(2, 3)]. The discussion of technical aspects of the then still new experimental microdosimetry took up a major part of the Symposium, i.e. detector design, interpretation of the results and general physical and dosimetric aspects.

The Symposia also offered the possibility to compare the different programmes of research in the field of microdosimetry developed in the USA, mainly in New York and in Europe and to stimulate collaborations. The presentation and discussion of conceptual and technical aspects of measurements with low-pressure tissue-equivalent proportional counters continued to be a focus in subsequent Symposia but increasingly the emphasis shifted towards the role of microdosimetry in radiation biology and its applications in radiation protection and radiation therapy. Alternative approaches to Rossi Counter microdosimetry such as the variance method[(4)] and recombination chamber dosimetry[(5)] were introduced, and computational methods such as track structure calculations began to play an important role.

In 1983, the ICRU published a report on Microdosimetry: Report 36[(6)]. It includes the definition of the microdosimetric quantities: the energy imparted ε, the lineal energy y and the specific energy z.

The 'Rossi counter' has been used for decades and new techniques were investigated. Recent developments include Rossi type proportional counters with simulated volumes smaller than 1 μm[(7)] and solid-state microdosimeters based on silicon[(8)] and single-crystal diamond detectors[(9)]. The latter work was as solid-state ionisation chambers. The prototypes range from 300 nm to 5 μm in thickness of diamond (d = 3.52 g cm^{-3}). An overview on experimental microdosimetric techniques and their application can be found in Braby (this Symposium).

Experimental microdosimetry confirmed that in the irradiated material, the energy is deposited

stochastically in small amounts ('event sizes') and provided a method to quantify the energy deposition distributions. Microdosimetric spectra, presented in terms of lineal energy, y, reveal the large dynamic range of energy depositions (Figures 2 and 3)[10, 11].

The spectra in Figure 2 have been measured for photons (and electrons) at different energies. For energies of >1 MeV up to all energies used in therapy, the microdosimetric spectra are similar to each other. No relative biological effectiveness (RBE) difference could thus be expected and actually no significant difference has been observed. These radiation qualities can thus be selected as a 'robust' reference for dosimetry, RBE and clinical studies.

The distributions are normalised per logarithmic interval and thus equal areas under the curve will contribute equally to the specific energy. Lindborg[10], cited in ICRU 36[6].

In contrast, significant differences in the microdosimetric spectra have been observed for X rays <1 MeV (Figure 3).

These differences correlate with differences in RBE observed in radiobiological experiments. In clinical practice, an RBE of 1.15 (Ref. ^{60}Co) was in the past recommended for 200 kV (conventional) X rays in therapy applications, but radiobiological data have shown RBE values up to 2–3 at low doses for some systems and endpoints[11, 12].

Figure 4 shows microdosimetric spectra for two neutron beams, which were used in fast neutron therapy, in comparison to a spectrum for ^{60}Co. The dynamic range of energy depositions is even larger than for photons. A comprehensive study of correlated microdosimetric measurements and radiobiological experiments at European neutron therapy facilities led to the derivation of an empirical biological weighting function $r(y)$[11, 13] (see Figure 5).

Although the derived weighting function reproduced the RBE values of the radiobiological experiments with a good statistical significance[13], the impact of this approach on clinical neutron therapy was low largely due to the lack of clinically relevant RBE values for different tissues.

Figure 1. Harald H. Rossi, Columbia University-New York, the pioneer of microdosimetry[1].

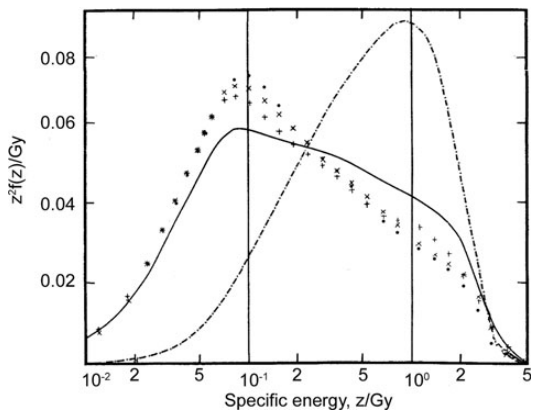

Figure 2. Microdosimetric spectra for beams of photons and electrons. Single-event specific-energy (z) distributions measured in five different beams, at the maximum of the depth-dose curves: (solid line) ^{60}Co γ rays. (dash dot line) 180 kV X rays with HVL = 09 mm Cu. (plus symbol) 42 MV photons. (dot line) 39 MeV electrons. (multiply symbol) 15 MeV electrons. The distributions are normalized per logarithmic interval and thus equal areas under the curves will contribute equally to the specific energy. Lindborg (1976)[10], cited in ICRU 36 (1983)[6].

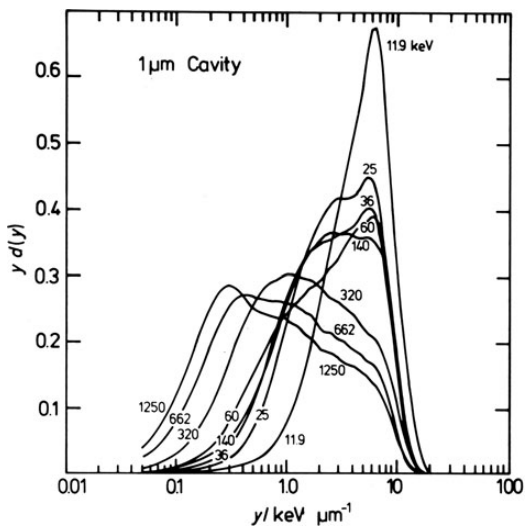

Figure 3. Microdosimetric spectra for monoenergetic X rays for 1 μm simulated diameter. Photon energy in keV as parameter, after Kliauga and Dvorak (1978), cited in ICRU Report 36[6].

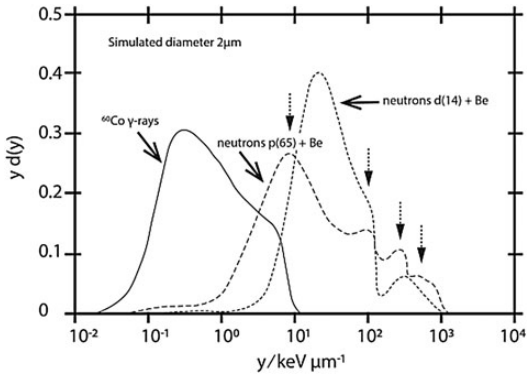

Figure 4. Comparison of the microdosimetric spectra $y\,d(y)$ vs. y obtained for ^{60}Co γ rays, d(14) + Be neutrons and p(65) + Be neutrons, i.e. the lowest and highest neutron energies applied for therapy[11, 13].

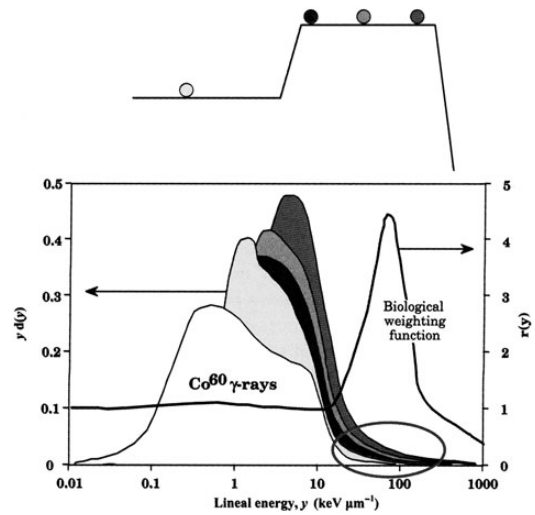

Figure 5. Microdosimetric spectra in a 90 MeV modulated-energy proton beam. Measurements are performed in the initial plateau, at the proximal, middle and distal positions in the Spread-Out Bragg Peak (SOBP) (as indicated on the top of the figure). The shift of the spectra towards higher y values with an increasing depth which correlates with the 10 % higher value of the proton RBE compared with the ^{60}Co.

MICRODOSIMETRY IN RADIOBIOLOGY

In the 15 Symposia on Microdosimetry, several biological models and their potential implications in radiation protection and therapy were presented and discussed based or derived from microdosimetry and results obtained in radiation physics research.

The 'Theory of dual radiation action' by Kellerer and Rossi[14, 15], which is based on microdosimetric data and concepts, was discussed intensively in several symposia in the 1970s. The theory, initially developed for radiation protection purposes, was extended to several types of applications, in particular, radiation therapy.

Today, the use of the linear-quadratic model in radiation therapy is reasonably well validated and influences all radiation therapy techniques. It is used to evaluate the effect of several factors on the clinical outcome such as the time factors and the radiation quality.

MICRODOSIMETRY IN PARTICLE-BEAM THERAPY

Microdosimetric measurements and data were used in the context of therapy with high-energy photons and electrons[10], with fast neutrons[11, 13, 16] and with negative pions[17]. Using this experience, microdosimetry is now also applied in particle therapy.

QUANTITIES, DEFINITIONS AND UNITS

Absorbed dose is the fundamental quantity in radiation therapy. When reporting radiation therapy procedures, it should always be reported together with the complete description of the irradiation conditions. The clinical effects depend, however, on radiation quality and several other factors including fractionation, overall treatment time, tumour type and location[18].

In order to account for all factors, ICRU has presented a clinically more relevant quantity: the equi-effective dose[19]. It is defined as the absorbed dose that, when delivered under different technical and irradiation conditions, produces the same probability of a specific endpoint as under the reference conditions.

The equi-effective dose is the product of the absorbed dose and a weighting factor which takes into account all factors listed above that can influence the biological/clinical effects. These factors have to be combined and are not independent from each other. At present, accounting for radiation quality is still using microdosimetric data but empirical information. The equi-effective dose and the absorbed dose are both expressed in Gy.

MICRODOSIMETRY IN PROTON-BEAM THERAPY

The main argument in favour of proton therapy is an improved physical selectivity (Bragg peak and finite range) compared with photon beams. No significant radiobiological benefit has to be expected compared with the modern photon techniques.

Radiobiological data show an increase of RBE ranging from 0 to 20 % relative to ^{60}Co. This is in agreement with the microdosimetric data[13, 20] (Figure 5). The ICRU recommends a generic RBE of 1.1 for clinical applications[21]. Although this recommendation

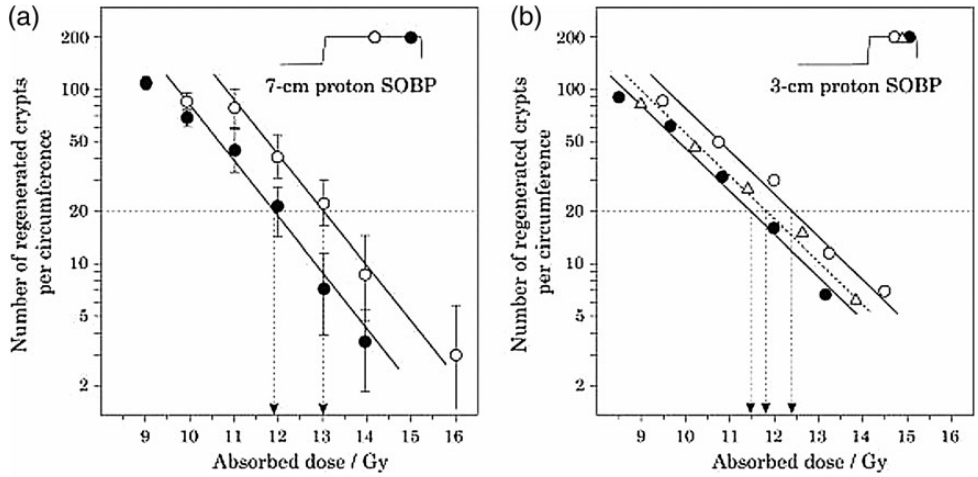

Figure 6. Dose–effect relationships for crypt regeneration in mice after irradiation at different depths in the iThemba 200 MeV clinical proton beam. (**a**) SOBP = 7 cm. The open and closed circles correspond to irradiations in the middle and end of the SOBP, respectively. Parallel exponential regression curves are fitted by the weighted least squares method (95 % confidence intervals). (**b**) SOBP = 3 cm. The same presentation. The triangles correspond to irradiations halfway between the middle and end of the SOBP[22].

seems justified, recent data have shown a further RBE increase between the middle and the end of the Spread-Out Bragg Peak (SOBP). Its clinical significance is still a matter of debate. An example for intestinal crypt cells is shown in Figure 6[22]. Accurate animal data and beam positioning allow one to irradiate part of the intestine at different depths of the SOBP.

The biological weighting function $r(y)$ (right ordinate) was obtained for intestinal crypt cells. The increase of the $r(y)$ function >10 keV μm^{-1} is related to the RBE increase at the distal SOBP region[13, 20].

MICRODOSIMETRTY IN CARBON-ION THERAPY

Like proton beams, carbon-ion beams have a high physical selectivity. In addition, from a radiobiological point of view, because they are high-LET radiation, the clinical results are less dependent on dose per fraction and relatively more effective for late than early effects[18]. They have LET and microdosimetric y spectra similar to fast neutrons as used in therapy (Figure 4). A clinical benefit could thus be expected for some tumour types (e.g. salivary gland and prostate tumours, slowly growing sarcomas)[23–25].

Evaluation and selection of RBE values and equieffective dose for prescribing, planning and reporting carbon-ion therapy is a complex issue. Two different irradiation techniques are used today: at NIRS in Japan, where passive scattering was used initially and in Darmstadt-Heidelberg, Germany, where a scanning-beam technique is used.

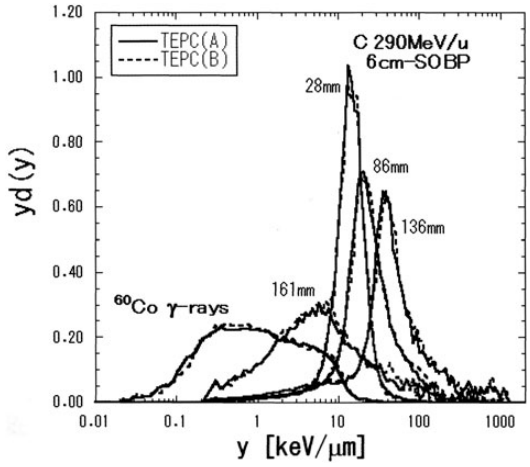

Figure 7. Microdosimetric spectra of lineal energy, $y\ d(y)$, measured for ^{60}Co and a 290 MeV u^{-1} carbon-ion beam (SOBP = 60 mm) at four typical depths: 28 mm (entrance), 86 mm proximal SOBP, 136 mm (rear SOBP) and 161 mm (fragmentation tail)[26].

At NIRS, a 'clinical RBE' of 3 is assumed for carbon ions at a point located 2/3 of the depth of the SOBP, where the local lineal energy y is $\sim$80 keV μm^{-1} (Figure 7)[26]. This RBE value of 3 was, in the past, the 'clinical RBE' adopted for fast neutron therapy in the NIRS experience. The microdosimetric spectra for fast neutron beams are wide but an average value of $\sim$80 keV μm^{-1} could be derived (Figure 4)[18]. The physical,

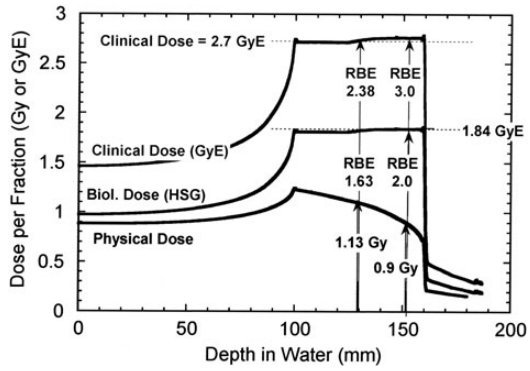

Figure 8. Depth–dose curves in a single 290 MeV u^{-1} carbon-ion beam with a 6 cm SOPB at NIRS Chiba-Japan. The doses per fraction are compared: the (physical) absorbed dose (lower curve), the 'biological' dose (dotted line) derived from radiobiological experiments (HSG: human salivary gland), the 'clinical' dose (upper solid line) based on clinical neutron data obtained at NIRS. The RBE variation in the SOBP is supported by a series of experiments performed at the Chiba facility[27].

radiobiological and clinical depth–dose curves are compared in Figure 8[27].

In Darmstadt-Heidelberg, where a scanning-beam technique is used, the equi-effective dose is computed point-by-point (voxel) in the target volume based on local LET, absorbed dose, dose per fraction and selected biological endpoint. For current treatment planning, the LEM model is used[28, 29].

CONCLUSION

The development of microdosimetry by Harald Rossi, in the 1960s, has contributed to the authors understanding of the biological effects of ionising radiations and influenced teaching programmes.

Absorbed dose is the fundamental quantity in radiation therapy and must always be reported. However, clinical effects depend also on other factors including radiation quality. In order to provide a pragmatic, empirical method for clinical practice, ICRU is proposing a quantity, the equi-effective dose.

When comparing different therapy beams, reporting clinical RBE values imply that the absorbed doses are accurately known and that the dose distributions in the target volume are comparable. This has been achieved only for selected radiobiological systems and techniques: few experimental protocols for this purpose have been published to date (cells *in vitro*, intestinal crypt cells *in vivo*). In existing clinical situations, the dose distributions are often not comparable (e.g. carbon-ion beams compared with photon irradiations), it is difficult to meet the required criteria.

Specification of radiation quality is of particular importance for therapy with particles, fast neutrons and ions. In spite of many years of research, microdosimetry has not yet provided a generally applicable method for accounting of radiation quality in particle therapy.

Earlier attempts to establish a microdosimetry-based method to account for radiation quality for fast neutron therapy were promising[13]. However, due to the paucity of clinically relevant radiobiological data and with the decline of the number of active neutron therapy facilities also the interest in using microdosimetric approaches to deriving clinical RBE declined.

However, renewed interest in using microdosimetry for radiation quality quantification has developed for therapy with C-ions[26, 30], where the clinical RBE varies significantly within and outside the treatment volume.

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